PATENT COOPERATION TREATY

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# PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| HERY 011 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/CA00/00003 | 05/01/2000 | 06/01/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/167 | | |
| Applicant<br>HENRY, RICHARD | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 24/07/2000 | 15.03.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Pilling, S<br>Telephone No. +49 89 2399 8461 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00003

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
**Description, pages:**

| | |
|---|---|
| 1-16 | as originally filed |

**Claims, No.:**

| | | | | |
|---|---|---|---|---|
| 1-14 | as received on | 24/07/2000 | with letter of | 17/05/2000 |

**Drawings, sheets:**

| | |
|---|---|
| 1/3-3/3 | as originally filed |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*
   **see separate sheet**

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-8,14.

because:

   ☒ the said international application, or the said claims Nos. 1-8,14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   **see separate sheet**

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

   Novelty (N) Yes: Claims 2,9-14

| | | | |
|---|---|---|---|
| | No: | Claims | 1,3-8 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-14 |
| Industrial applicability (IA) | Yes: | Claims | 9-13(for Claims 1-8,14 see the comments under Item V on separate sheet) |
| | No: | Claims | |

2. Citations and explanations
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:
**see separate sheet**

**Re Item I**
**Basis of the opinion**

1. The amendments filed with the letter dated 17th May 2000 introduce subject matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following;

   a) The reference in Claims 1 and 14 to the alkalinizing agent being provided in sufficient quantity to raise the pH of the bladder "*to approximately the pKa of the local anesthetic*"; in this regard, it is noted that the originally filed description indicates (i) that it would in general be desirable that the intra-vesical pH be elevated "*closer to the pKa of the local anesthetic*" (see page 8 lines 17 to 20); (ii) each local anaesthetic has an optimum basic pH for absorption (see page 7 lines 7 to 10) and; (iii) in the case of lidocaine it would seem that the optimum pH range for absorption, *i.e.* pH 8.0 to 8.3 (see page 14 line 26 to page 15 line 5 and Table 1) is slightly above the pKa for lidocaine (pH 7.9) (see page 9 lines 6 to 15) Nevertheless, there is no disclosure that there is a link between the optimum pH for absorption and the pKa and there seems to be no clear teaching in this document that in every case, *i.e.* under all conditions and with all local anaesthetics, the intra-vesical pH should be raised to approximately the pKa of the local anaesthetic.

   b) the definition in Claim 13 that a "*quantity of alkalinizing agent is 5 to 50 ml of 2-20% sodium bicarbonate*"; in this regard, the originally filed description only appeared to disclose a concentration range of bicarbonate of from "*2-10%*" (see page 12 lines 27 to 29).

   c) the method of Claim 14 that involves *"the steps of periodically administering to a patient..Etc*"; in particular no reference to periodic administration can be found in the originally filed description.

2. Hence, the amendments identified above have not been taken into account when making the following assessment of novelty and inventive step of the claims.

**Re Item III**
**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

3. Claims 1 to 8 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**
**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

4. The present application relates to methods for anaesthetizing a patient's bladder using a local anaesthetic in combination with an alkalinizing agent (Claims 1 to 8); pharmaceutical combinations for anaesthetizing a patient's bladder comprising a local anaesthetic and an alkalinizing agent in a syringe (Claims 9 to 13) and methods of treating interstitial cystitis using a local anaesthetic in combination with an alkalinizing agent (Claim 14).

5. Claims 1 to 8 and 14 relate to methods of treatment of the human or animal body by therapy (see present page 1 lines 12 to 17), surgery (see present Claim 3) and diagnosis (see present page 9 lines 16 to 17). In this regard, for the assessment of these claims with respect to industrial applicability, no unified criteria exist in the PCT. Furthermore, patentability can be dependent on the formulation of the claims. The EPO, for example does not recognize as industrially applicable, the subject matter of claims directed to a method of treatment of the human or animal body or to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D4 as follows;

   D1: British Journal of Urolology (1979) 51(6) 500-503

D2: British Journal of Urolology (1987) 60(6) 516-518

D3: The Journal of Pharmacology and Experimental Therapeutics (1965) 150(1) 152-159

D4: Scandinavian Journal of Urology and Nephrology (1994) 28 (4) 359-64

D5: *US-A-5137528

D6: *BIOSIS Abstract Accession No 0692950 & Asklin B *et al*, Scand. J. Urol. Nephrol. 23(4), 1989, pp 311-312

* documents D5 and D6 were known to the International Preliminary Examining Authority and copies are enclosed herewith

Claims 1 to 8; methods for anaesthetizing a patient's bladder

7. Document D1 discloses that detrusor instability can be treated by anaesthetising the bladder of the patient. This anaesthetic treatment is performed by introducing 40 ml of 1% lignocaine solution with 40 ml of an 8.4% solution of sodium bicarbonate through a urethral catheter into the bladder (see the "*Patients and Methods*" on pages 500 to 501 of D1).

8. Document D2 similarly discloses treatment of patients with detrusor instability by filling the bladder with lignocaine hydrochloride in bicarbonate solution (see the "Patients and Methods" on page 516 of D2).

9. Thus, the subject matter of Claims 1 and 3 to 8 is not new in view of the disclosures of each of documents D1 or D2 (Article 33(2) PCT).

10. None of the documents appears to disclose a method according to present Claim 2 wherein the local anaesthetic and alkalinizing agent are provided to the bladder separately.

11. Thus, the subject matter of Claim 2 is new (Article 33(2) PCT).

12. The closest prior art in respect of Claim 2 is considered to be document D1. As indicated herein above, this document discloses treatment of detrusor instability by intra vesical instillation of lignocaine and sodium carbonate. It is further noted that this document indicates that sodium bicarbonate is necessary in order to achieve alkalinization of the bladder contents for the most effective action of the lignocaine solution. (see the "Discussion" on pages 502 to 503 in D1). This document does not, however, clearly disclose if the lignocaine and sodium bicarbonate solution were introduced separately or together.

13. It is considered however that separate administration of the local anaesthetic and alkalinizing agent as set out in Claim 2 is insufficient to confer inventive step on the subject matter of this claim. In this regard, it seems that administration of said local anaesthetic and alkalinizing agent must either be carried out together or separately and that there is no surprising technical effect resulting from either of these alternative modes of administration.

14. Thus, the subject matter of Claim 2 is not inventive in view of the disclosure of document D1 (Article 33(3) PCT).

Claims 9 to 13 combinations for anaesthetizing a patient's bladder

15. For reasons substantially as set out in respect of Claim 2 (see herein above), it is considered that the subject matter of Claims 9 to 13 is new (Article 33(2) PCT) but is not inventive in view of the disclosure of document D1 (Article 33(3) PCT). In this regard, as indicated above it is considered that methods of anaesthetizing the bladder via separate instillation of local anaesthetic and alkalinizing agent into the bladder are obvious. Present Claim 9 merely appears to relate to a conventional single use disposable syringe that has been adapted to carry out the obvious method of Claim 2. This adaptation is considered to be routine and makes no inventive contribution to the present art.

16. In support of the above comments, the Applicant's attention is drawn to the disclosure of document D5 that describes a syringe comprising both a local

anaesthetic and an alkalinizing agent.

Claim 14; methods for treating interstitial cystitis

17. None of the presently cited documents disclose methods of treating interstitial cystitis using a local anaesthetic in combination with an alkalinizing agent. Thus, the subject matter of Claim 14 is new (Article 33(2) PCT).

18. The following comments are however relevant to lack of inventive step of Claim 14; document D6 shows that treatment of interstitial cystitis using a local anaesthetic, *i.e.* lidocaine is known. In view of the teaching in each of documents D1 or D2 that the optimal anaesthetic effect is achieved at an alkaline pH, it is considered obvious to add an alkalinizing agent to the treatment of document D6. In this regard, the improved effects of the new treatment, *i.e.* enhanced anaesthetic effect could have been predicted by one skilled in this art with reference to either of documents D1 or D2.

19. Thus, the subject matter of Claim 14 is not inventive in view of the disclosure of document D1 (Article 33(3) PCT).

**Re Item VII**
**Certain defects in the international application**

20. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.